Translation

PCT/EP2003/003097

PATENT COOPERATION TREATY

PCT

Rec'd PCT/PTO 27 SEP 2004

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 96099 a/se	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/003097	International filing date (*day/month/year*) 25 March 2003 (25.03.2003)	Priority date (*day/month/year*) 26 March 2002 (26.03.2002)
International Patent Classification (IPC) or national classification and IPC A61K 35/78, A61P 25/18		
Applicant LICHTWER PHARMA AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 October 2003 (20.10.2003)	28 June 2004 (28.06.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/003097

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-17, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-13, filed with the letter of 13 May 2004 (13.05.2004)

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-13	YES
	Claims		NO
Inventive step (IS)	Claims	1-13	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims		NO

2. Citations and explanations

1a. The present application relates to the use of *Hypericum perforatum* (St John's wort) and/or *Ginkgo biloba* (ginkgo) and/or *Crocus sativus* (safron) and/or *Panax ginseng* (ginseng) for the treatment of schizophrenia (see main claim 1).

1b. Despite existing transitional forms and mixed conditions in the symptomology of schizophrenia and depression, schizophrenia as a **classic psychotic disorder** should be distinguished from depression as a **classic neurotic disorder**. A scientifically acknowledged basis for this distinction is to be found in ICD-10 (The International Statistical Classification of Diseases and Related Health Problems), in which schizophrenia is distinguished from other classified conditions such as dementia and depression. Consequently, a distinction must be drawn between substances indicated in schizophrenia and substances indicated in depression.

2. In this light, the prior art cited in the written report, relating to the treatment and prophylaxis of depressive disorders or dementia, requires revision.

/...

D1 (EP-A-1 034 782) relates to the treatment of depression, which is distinguished from schizophrenia along the lines set out in point 1b. above, being a psychiatric condition the genesis of which is different from that of schizophrenia.

D2 (US-A-6 083 932) discloses an extract of ginseng (HT1001) for the treatment of conditions coming under the generic heading of dementia, and also for the treatment of Parkinson's disease, attention-deficit syndrome, strokes and depression. However, according to ICD-10 these conditions are not classified under the psychotic disorder of "schizophrenia" - and, therefore, are not within the scope of the present application.

D3 (WO-A-0 004 912) relates to the use of a ginseng extract for the treatment of dementia, referring in particular to improved learning and memory. However, schizophrenia is clearly defined as a different disease from dementia.

D4 (WO-A-9 966 914) discloses a combination of *Hypericum* and L-carnitine for the prophylaxis and treatment of anxiety or depression; in the light of the above remarks, said combination is not within the scope of the present application.

D5 (WO-A-9 940 905) discloses the use of hyperforin and extracts containing hyperforin for the treatment and prophylaxis of dementing diseases. The use thereof in schizophrenia is not disclosed in said document, nor is it obvious therefrom.

D6 (EP-A-599 307) relates to a *Hypericum* extract containing a raised level of hypoforin for use as a psychovegetative and anti-depressant drug. However, the use in schizophrenia as per the claims of the present application does **not** concern a pyschovegatively conditioned dysfunction or depression.

D7 (WO-A-0 002 455) discloses the specific effect of hypericin on the blocking of T-type calcium channels, which is important in the treatment of depressive conditions but is not included in the management of schizophrenia since schizophrenia is not classed as a disorder of the type treated with T-type Ca antagonists.

D8 (DE-A-3 338 995) relates to the use of bilobalid for the treatment of degenerative cerebral disorders which are accompanied by pathological changes in the myelin layer of the nerve fibres. Schizophrenia, however, is **not** a degenerative disorder of the brain or the nervous system.

3. In the light of the aforementioned documents, it can be conclusively established that the subject matter of the present application is neither disclosed in nor otherwise obvious from the prior art. The requirements of PCT Article 33(2) and PCT Article 33(3) are accordingly satisfied.

Amended Patent Claims as Filed on May 13, 2004

1. Use of *Hypericum perforatum* (St John's wart) and/or *Ginkgo biloba* (ginkgo) and/or *Crocus sativus* (saffron) and/or *Panax ginseng* (ginseng) for the production of a medicament for the treatment of schizophrenia.

2. Use according to claim 1, wherein the plant, plant parts, dried plant or plant parts, extracts, extract fractions, pure substances and their derivatives and the salts of the plant are used.

3. Use according to one of the preceding claims, wherein the extract used is an alcoholic, alcoholic-aqueous extract with primary, secondary and tertiary alcohols of the series C1 to C5, preferably methanol and ethanol, in the composition of alcohol/water of between 100/0 to 30/70, preferably 80/20 to 50/50.

4. Use according to claim 3, wherein these are produced in a one- and multi-step production process.

5. Use according to one of claims 1 to 4, wherein the St John's wart extract used has the following amounts of components: 0.01 – 2% hypericins, 0.01 – 30% hyperforins, 2 – 35% flavonoids, preferably 0.10 to 0.40% hypericins and 1 – 6% hyperforins.

6. Use according to one of claims 1 to 4, wherein the gingko extract has the following amounts and components: 20 to 30% by weight flavone glycosides, together with 2 – 8% of ginkgolides, particularly preferred 23 to 27 % flavone glycosides and 5 to 7% by weight ginkgolides.

7. Use according to one of claims 1 to 4, wherein the saffron extract comprises the components α-, β-pinene, 1,8 cineol, crocin, picrocrocin as well as optionally the degradation product thereof safranal, particularly preferred in the following concentrations: 5 – 10% pinene and cineol, 4 – 10% picrocrocin and/or 2 – 6% safranal.

8. Use according to one of claims 1 to 4, wherein the ginseng root extract comprises the components, *inter alia*, triterpene saponines (ginsenosides/ginsenoids), sesquiterpenes and polyacetylenes, particularly preferred in the following concentrations: 3 – 9% ginsenoids.

9. Use according to one of the preceding claims, wherein use occurs in the form of liquid, semi-solid and solid forms of administration, in particular solutions, suspensions, tablets, film-coated tablets, dragees, capsules, effervescent tablets, effervescent granulate, chew tablets and suppositories.

10. Use according to one of the preceding claims, wherein in the case of St John's wart extract, the daily dose of the extracts is 300 to 2700 mg in up to 3 separate doses per day, preferably 750 – 1500 mg in 1 – 2 separate doses per day.

11. Use according to one of the preceding claims, wherein in the case of *Gingko biloba*, *Crocus sativus* and *Panax ginseng*, the daily dose of the extracts is 50 mg – 1000 mg of extract.

12. Combination preparation containing St John's wart, gingko, saffron and/or ginseng in addition to, as further components, a psychotherapeutic drug against schizophrenia for the simultaneous, separate or graduated use in the treatment of schizophrenia.

13. Use according to one of claims 1 to 11 in add-on therapy in combination with psychotherapeutic drugs for treating schizophrenia, in particular neuroleptics, in particular of the group of classic neuroleptics such as haloperidol, benperidol, chlorprotixene, flupentixol, fluphenazine, perazine, perphenazine, thioridazine, atypical neuroleptics, in particular clozapine, olanzapine, seroquel, sertindole, as well as other psychotherapeutic drugs suitable for treating schizophrenia.